REMARKS

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78 are pending in the application.

Supplemental Information Disclosure Statement

Applicants file concurrently herewith a Supplemental Information Disclosure Statement ("SIDS") for the Examiner's consideration.

Rejection of Claims Under 35 U.S.C. § 101

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78 are rejected under 35 U.S.C. § 101 as not supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse the rejection for the reasons of record set forth in the responses filed on January 2, 2004 and October 19, 2004 and for the further reasons discussed in detail below.

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78 are directed to recombinant yeast cells comprising a recombinant gene encoding a heterologous orphan G protein-coupled receptor wherein the receptor is expressed on the cell membrane of the cell such that signal transduction activity is modulated by interaction with an extracellular signal; and a recombinant gene encoding a heterologous test polypeptide, wherein the test polypeptide is transported to a location allowing interaction with the receptor expressed on the cell membrane. The yeast cells are "autocrine" in that they are engineered to express the polypeptides to be tested for the ability to modulate the orphan G protein-coupled receptors expressed by the yeast cells. A collection of such yeast cells can be used to express a library of test polypeptides. The claimed recombinant yeast cells are used in screening assays to identify compounds, *e.g.*, ligands, that modulate the orphan G protein-coupled receptors expressed by the yeast cells.

The Examiner has rejected the claims as not supported by either a specific and substantial asserted utility or a well-established utility, citing the reasons of record. The Examiner additionally objects to the Applicants' response of October 19, 2004 on the grounds that the "instant invention lacks specific and substantial real world utility absent

elucidation of the biological function of the orphan receptor and any role that the ligands identified as modulators of the receptor would play in modulation or identification of any disease state associated with that biological function." (December 9, 2004 Office Action, page 3, middle paragraph.) The Examiner cites *Brenner v. Manson*, 383 U.S. 519 (1966) to support the rejection.

It is respectfully submitted that *Brenner v. Manson*, 383 U.S. 519 (1966) held that a novel chemical process lacked utility where the resulting product was not known to have any biological activity. Biological activity of the product in question was, at best, yet to be determined. Application of the rule in *Brenner* is therefore reserved for inventions that lack biological function, which is not the case for the present invention. The G protein-coupled receptors of the present invention have well-known biological functions that are described in detail below.

G protein-coupled receptors are structurally and functionally related proteins characterized by seven membrane-spanning alpha helices, an N-terminal segment on the exoplasmic face and a C-terminal segment on the cytosolic face of the plasma membrane. G.M. Cooper, *The Cell A Molecular Approach*, Chapter 13, 2nd edition (Sinauer, 2000) (copy enclosed with SIDS). This large receptor family includes light-activated receptors (rhodopsins) in the eye and odorant receptors in the mammalian nose, as well as numerous receptors for various hormones and neurotransmitters. Although these receptors are activated by different ligands and may produce different cellular responses, they all mediate a similar signaling pathway. H. Lodish, *et al.*, *Molecular Cell Biology*, Chapter 20.3 (W. H. Freeman and Company, 2000) (copy enclosed with SIDS).

All G protein-coupled receptors follow the same functional paradigm. The binding of ligands to the extracellular domain of G protein-coupled receptors induces a conformational change that allows the cytosolic domain of the receptor to bind to a G protein associated with the inner face of the plasma membrane. G proteins consist of three subunits, designated α, β, and γ. This interaction activates the G protein, which then dissociates from the receptor and carries the signal to an intracellular target or "effector." Essentially, dissociation of the G-protein heterotrimer into G_α and $G_{\beta\gamma}$ units

transmits the signal that the receptor has bound its ligand. G.M. Cooper, *The Cell A Molecular Approach*, Chapter 13, 2nd edition (Sinauer, 2000).

All G protein-coupled receptor ligand binding activates a G protein, which in turn activates or inhibits an effector that generates a specific second messenger or modulates an ion channel, causing a change in membrane potential. Adenylyl cyclase, which catalyzes the formation of cAMP from ATP, is the best-characterized effector regulated by trimeric G proteins. All adenylyl cyclase isoforms are stimulated by $G_{s\alpha}$, and certain isoforms are inhibited by $G_{i\alpha}$ and $G_{\beta\gamma}$. $G_{s\alpha}$, $G_{i\alpha}$ and $G_{\beta\gamma}$. As a result, adenylyl cyclase is regulated by G protein-coupled receptors and is stimulated or inhibited by many different G protein-coupled receptor ligands. H. Lodish, *et al.*, *Molecular Cell Biology*, Chapter 20.1 and 20.3 (W. H. Freeman and Company, 2000) (copy enclosed with SIDS).

G protein-coupled receptors, including those of the present invention, enable ligands to trigger G protein activation to modulate the activity of an effector (e.g., adenylyl cyclase) and therefore, have a common biological function. Thus, identification of ligands that signal or inhibit signaling through G proteins is specific and substantially useful for the modulation of this kind of intracellular biological response. *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985).[1]

It appears that the Examiner discounts the fact that the claimed invention is directed to a well-known class of receptors and instead rejects the invention simply on the grounds that the receptors are "orphan receptors." Although acknowledging that "[o]rphan receptors have been conserved in evolution and are distributed throughout the body like other known receptors, and are therefore, clearly involved in human biological function" (December 9, 2004 Office Action, page 5, first full paragraph), the Examiner implies that this assessment represents the extent of knowledge available for any orphan receptor. Such generalization is improper, as the orphan receptors of the present invention are known to be G protein-coupled receptors and therefore, are known to possess the inherent biological functions, *e.g.*, regulation of adenylyl cyclase, that are common to this particular class of receptor.

[1] Compounds with a demonstrated pharmacological activity in vitro have utility.

The Examiner further alleges that the receptors of the present invention are without an elucidated biological function and as a result, cannot be tied to any role in modulation or identification of any disease state associated with a biological function. Quite to the contrary, many essential metabolic pathways are dependent upon G-protein coupled receptor modulation of adenylyl cyclase. In the liver, glucagon and epinephrine bind to different G protein-coupled receptors, but binding of both hormones activates adenylyl cyclase and thus triggers the same metabolic responses. In adipose cells, for example, epinephrine, glucagon, and ACTH all stimulate adenylyl cyclase. Molecular Cell Biology, Chapter 20.3 (W. H. Freeman and Company, 2000) Through their common functionality, G protein-coupled receptors enable different receptor-hormone complexes to modulate the physiological activity of adenylyl cyclase in many types of cells, which is a further demonstration of their specific and substantial utility. *Fugiwaka v. Wattansin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996).[2]

Given the importance of G protein-coupled receptors in the regulation of essential metabolic pathways, it logically follows that the improper regulation of adenylyl cyclase can give rise to specific disease states. In human genetics, activating mutations that modify cellular signaling responses quite often produce dominant phenotypes. Mutations in the G-protein coupled receptors provide several examples of such dominant phenotypes. As described above, many hormones exert their effects on target cells by binding to the extracellular domains of transmembrane receptors. Binding of ligand causes the cytoplasmic tail of the receptor to catalyze conversion of an inactive (GDP-bound) G-protein into an active (GTP-bound) form, and this relays the signal further by stimulating adenylyl cyclase. T. Strachan, *et al.*, *Human Molecular Genetics*, Chapter 16 (BIOS Scientific Publishers, Ltd, 1999) (copy enclosed with SIDS). Some mutations cause receptors to activate adenylyl cyclase even in the absence of ligand:

[2] In the pharmaceutical arts, it has long been held that practical utility may be shown by adequate evidence of **any** pharmacological activity.

- Familial male precocious puberty (OMIM 176410: onset of puberty by age 4 in affected boys) is found with a constitutively active luteinizing hormone receptor.

- Autosomal dominant thyroid hyperplasia can be caused by an activating mutation in the thyroid stimulating hormone receptor (see OMIM 275200).

- Jansen's metaphyseal chondrodystrophy (OMIM 156400: a disorder of bone growth) can be caused by a constitutionally active parathyroid hormone receptor.

- A constitutionally active $G_{s\alpha}$ protein (part of the G-protein) causes McCune-Albright syndrome or polyostotic fibrous dysplasia (PFD, OMIM 174800). PFD is known only as a somatic condition in mosaics - probably constitutional mutations would be lethal. Depending on the tissues carrying the mutant cell line, the result is polyostotic fibrous dysplasia, café- au-lait spots, sexual precocity and other hyperfunctional endocrinopathies. Loss of function mutations of the same gene often underlie a different disease, Albright's hereditary osteodystrophy. Human Molecular Genetics, Chapter 16 (BIOS Scientific Publishers, Ltd, 1999).

Brenner does not require, as the Examiner suggests, that the biological activity must be associated with the modulation or identification of "a disease state." Nonetheless, several human genetic defects are known to be caused by defects in G protein-coupled receptor signaling. Therefore, identification of G protein-coupled receptor ligands according to methods of the invention can give rise to previously unknown ligands that beneficially modulate these and other disorders associated with G protein-coupled receptor signaling. This also represents a utility that is specific and substantial.

Again, it is brought to the Examiner's attention that screening assays are one of the categories of inventions that M.P.E.P. §2107.01 specifically lists as having "a clear, specific and ***unquestionable*** utility (*e.g.*, they are useful in analyzing compounds)." (Emphasis added.) The utility of the claimed yeast cells lies in their ability to screen for and identify ligands that modulate the surrogate yeast signal transduction activity as described above. The singular result of identifying such ligands is useful under § 101 for modulation of the signal transduction activity.

In rebutting a *prima facie* showing of lack of utility, an applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 U.S.P.Q. 351, 354 (C.C.P.A. 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. It is respectfully submitted that the evidence of record, which includes not only the scientific facts provided herein but also numerous accounts from the pharmaceutical industry, more than fulfills the Applicants' burden of proof.

The following section of the M.P.E.P. provides further guidance on the subject:

> **2107 Guidelines for Examination of Applications**
>
> An invention has a well established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.... If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."
>
> ***A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record.*** Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered. (emphasis added).

Applicants further submit that those of ordinary skill in the art recognize the utility of the claimed invention based on the benefit of identifying ligands of orphan G protein-coupled receptors. This is particularly true in view of the scientific evidence presented herein as well as the PharmaVitae 2003 (Datamonitor) and RECAP alliance summaries submitted with Applicants' October 19, 2004 response.

Thus, the assertion of utility would be considered credible by a person of ordinary skill in the art, based upon relevant facts establishing that the claimed invention is associated with a well-known biological function and is useful for the identification of ligands that modulate that function. Therefore, in accord with the M.P.E.P. and applicable case law, an asserted utility has been provided for the claimed invention that is specific, substantial, and credible, and would be considered as much by a person of ordinary skill in the art in view of all evidence of record. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse the rejection for the reasons of record and reiterate those reasons herein, and for the additional reasons detailed below.

The Examiner has rejected the claims as not supported by "sufficient guidance to enable one of skill in the art to be able to use the claimed yeast cells or the receptor ligand for any diagnostic or therapeutic purpose without undue experimentation." The Examiner appears to maintain the allegation that because the invention as claimed does not have utility, a person skilled in the art would not be able to use the invention as claimed without undue experimentation, and as such, the claim is defective under 35 U.S.C.§ 112, first paragraph.

In this regard, M.P.E.P. § 2164.07 provides that a 35 U.S.C. § 112, first paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. § 101. For the reasons of record set forth in the responses filed on January 2, 2004 and October 19, 2004 and for the further reasons

discussed in detail above it is respectfully submitted that the rejection under 35 U.S.C. § 101 is improper and should be withdrawn.

M.P.E.P. § 2164.07 further provides that any rejection under 35 U.S.C. § 112, first paragraph, based on grounds other than "lack of utility" should be imposed separately from any rejection imposed due to "lack of utility" under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph. The grounds for rejection given by the Examiner (December 9, 2004 Office Action, page 6, paragraphs1-3.) do not appear to include any basis other than the alleged lack of utility. Applicants maintain that such grounds for rejection are improper and therefore, respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. § 103

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78 remain rejected under 35 U.S.C. § 103 as being unpatentable over King *et al.* (*Science* 250:121. 1990) in view of Devlin *et al.* (*Science* 249:404-406, 27 Jul. 1990), Scott et al. (*Science* 249:386-390, 27 Jul. 1990), and Cwirla et al. (*P.N.A.S.* 87:6378-6382, Aug. 1990) and Ladner *et al.* patent (U.S. Pat. Ser. No. 5,096,815) for the reasons of record. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

The Examiner relies on the King *et al.* publication as teaching the construction of a yeast cell of the species *Saccharomyces cerevisiae* which expresses a human beta2-adrenergic receptor, which is a heterologous G-protein-coupled receptor, a heterologous Gα subunit of a G protein which places the endogenous pheromone response pathway under the control of the heterologous receptor and a lacZ reporter gene under the control

of the pheromone responsive FUS1 gene promoter. The Examiner continues that King *et al.* also teach that "the ability to control the yeast pheromone response pathway by expression of a heterologous adrenergic receptor and its cognate G protein α subunit may facilitate structural and functional characterization in yeast of mammalian G protein coupled receptors. By scoring for growth arrest or β-galactosidase induction, the functional properties of mutant receptors can now be rapidly tested' and 'as additional genes for putative G protein-coupled receptors are isolated, numerous ligands can be screened to identify those with activity toward previously unidentified receptors". The Examiner clearly admits that "King *et al.* fail to teach yeast cells that express a variegated population of receptor effector polypeptides to be tested endogenously".

The Examiner relies on each of Devlin *et al.*, Scott *et al.* and Cwirla *et al.* references as teaching construction of random peptide libraries on phage for screening to identify ligands, e.g., ligands for hormone receptors and enzymes.

The Examiner relies on Ladner *et al.* as teaching screening for DNA-binding proteins by variegation of genes encoding known binding proteins and selection for proteins binding the desired target DNA sequence.

The Examiner maintains that it would have been obvious to one having ordinary skill in the art as the time the invention was made to construct a library of random peptides as taught by Devlin *et al.*, Scott *et al.*, Cwirla *et al.* or Ladner *et al.* in the yeast cells taught by King *et al.* to produce a mixture of recombinant yeast cells containing an expressible recombinant gene encoding a heterologous cell surface receptor and an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide with a reasonable expectation of success. Applicants respectfully traverse the rejection for the reasons of record set forth in the responses filed on January 2, 2004 and October 19, 2004 and for the further reasons discussed in detail below.

For reasons discussed in further detail below, the Examiner has failed to establish a prima facie case of obviousness because there was neither a suggestion in the prior art to combine the references in the manner proposed by the Examiner to arrive at the claimed invention, nor was there a reasonable expectation of success at the time the

invention was made. Furthermore, the proposed combination of references neither teaches nor suggests each and every element of the invention as claimed.

In reply to the Final Office Action dated April 19, 2004, Applicants' response of October 19, 2004 established rebuttal facts relevant to the lack of reasonable expectation of success in the cited references and the failure of the cited references to teach or suggest each and every element of the claimed invention. (October 19, 2004 Office Action, pages 22-26.) The Examiner failed to respond to Applicants' rebuttal. M.P.E.P. § 2142 is brought to the attention of the Examiner:

> When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the ***totality*** of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached. [Emphasis added.]

The Examiner's attention is further drawn to pages 18 – 22 of the present response, where Applicants have reiterated their position with respect to these points. The Examiner is respectfully requested to provide reasoning for maintaining the rejection in view of the totality of the evidence submitted by the Applicants, including that which is submitted on pages 19 – 23 of the present response (and which reiterates the arguments set forth on pages 22-26 of Applicants' response of October 19, 2004) .

I. Lack of Motivation/Suggestion

A. Combination of King and Devlin/Scott/Cwirla

The Examiner relies on the combination of King *et al.* and Devlin/Scott/Cwirla to provide the suggestion to use the King system, in which GPCR are expressed on yeast cells, to screen a library of random peptides to thereby identify receptor agonists or antagonists. However, at the time the invention was made, the ordinarily skilled artisan would not have been motivated to combine the teachings of King *et al.* and

Devlin/Scott/Cwirla because even if combined, the random peptide libraries of Devlin/Scott/Cwirla cannot be used in the system of King *et al.*

The system of King *et al.* utilizes yeast cells that express a heterologous GPCR in their cell membrane. As is well known in the art, the cell membrane of yeast is surrounded by a cell wall. When considering King in combination with Devlin/Scott/Cwirla, it would have been readily apparent to the ordinarily skilled artisan that one could not utilize the random peptide libraries expressed on phage taught by Devlin/Scott/Cwirla in the system of King *et al.* because the phage expressing the peptides would be unable to cross the yeast cell wall and therefore would be unable to gain access to the heterologous GPCR expressed on the yeast cell membrane. Because the peptide libraries of Devlin/Scott/Cwirla could not interact with the GPCRs of King *et al.*, the ordinarily skilled artisan would not have been motivated to combine the teachings of these references.

In reply, the Examiner states that King et al. "do teach modification of NH2-terminal of hß-AR gene for expression in the cell membrane of yeast." This teaching, however, does not cure the defects of the Devlin/Scott/Cwirla phage system, the use of which would fail to introduce a peptide library into the yeast cells of King et al. The Devlin/Scott/Cwirla phage systems requires that the phage be able to pass through the host cell wall in order to introduce the peptide library. The phages of Devlin/Scott/Cwirla would be unable to cross the yeast cell wall of King et al. and therefore, unable to express the peptide library within the yeast cells of King et al. Accordingly, one of skill in the art would not be motivated to combine the yeast system of King et al, with the phage systems of Devlin/Scott/Cwirla, as such a combination could not give rise to the claimed invention.

B. Combination of King and Devlin/Scott/Cwirla and Ladner

The Examiner further relies upon Ladner *et al.* for the motivation to express the random peptide library within the yeast cell. However, for various reasons discussed below, the ordinarily skilled artisan would not have been motivated to combine the teachings of King and Devlin/Scott/Cwirla with Ladner *et al.*

First, Ladner *et al.* explicitly teaches away from the practice of using yeast cells as the host cell for intracellular library expression. For example, Ladner *et al.* state that ***"[b]acterial cells are preferred over yeasts***, fungi, plant, or animal cells ***because they are superior on every count"*** (see column 22, at line 32; emphasis added). Ladner *et al.* further teach that because of the low efficiency of DNA uptake into yeast cells they are ***"not now preferred for the process described in this patent. . . . "*** (see column 24, at line 1; emphasis added). Although Ladner *et al.* state that the uses of "yeasts and mammalian systems are described further below" (see column 22, at line 39), Applicants have found no such teachings in the Ladner *et al.* reference disclosing how to successfully express peptide libraries in an "autocrine" fashion as in the yeast cells of the invention. Moreover, Ladner *et al.* do not describe or exemplify ***screening*** of a library in yeast cells. Furthermore, at column 85, line 14 under "Choice of Cell Line or Strain", Ladner *et al.* teaches only bacterial cells.

In reply, the Examiner alleges that Ladner *et al.* do not teach away from the use of yeast cells, but instead, teach that the "decisive experiments" should be carried out in eukaryotic cells such as yeast or Chinese hamster ovary cells. This is an inaccurate characterization of the teaching at column 22, lines 46-52, which states

> Because the intended use of the novel DBPs will often be in eukaryotic cells, some final development and testing may be done in eukaryotic cells such as Saccharomyces cerevisiae or Chinese hamster ovary cells. Genes that code on expression for DBPs that have been shown to work in bacterial cells will be introduced into eukaryotic cells to demonstrate that each DBP functions. Only limited variegation, however, can be used because, to date, the transformation systems for eukaryotic cells are, at best, 1000-fold less efficient than those used in E. coli K-12.

First, the above-referenced experiments are optional and not "decisive" as stated by the Examiner. Second, even in proposing the option of additional testing in eukaryotic cells, Ladner *et al.* continues to discourage and teach away from the use of eukaryotic cells by warning of the difficulties associated with such use. Third, in providing this characterization, the Examiner has failed to consider Ladner *et al.* as a whole. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would

lead away from the claimed invention. *W. L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed.Cir.1983), *cert. denied*, 469 U.S. 851 (1984). Thus, a complete reading of Ladner *et al.* would fail to provide one of ordinary skill in the art with any motivation or suggestion for combination with King and Devlin/Scott/Cwirla and more accurately, teaches away from the claimed invention.

II. Lack of Reasonable Expectation of Success

In addition to the foregoing, a *prima facie* case of obviousness has not been established because there was no reasonable expectation of success in making the claimed invention.

As discussed above, the pending claims pertain to methods of using recombinant cells, in which several different components are expressed by the cells and in which a variety of functional interactions are achieved. In particular, in the system of the invention of the claims presented herein, the heterologous orphan cell surface receptor is "expressed on the cell membrane of said cell such that signal transduction activity via said receptor is modulated by interaction with an extracellular signal." Additionally, the test polypeptide co-expressed in the cell is "transported to a location allowing interaction with the receptor expressed on the cell membrane." Still further, the mixture cells expresses a library of polypeptides wherein "modulation of the signal transduction activity of the orphan cell surface receptor by one of the heterologous test polypeptides within the library that reacts with said orphan cell surface receptor will provide a detectable signal."

At the time the invention was made, there simply was no reasonable expectation that each of these elements could be achieved to create successfully a system that detects a functional interaction between a heterologous orphan cell surface receptor expressed on a cell and a test polypeptide within a library that is expressed by the cell in an autocrine fashion. In fact, the teachings of the prior art provide several reasons that indicate that one of ordinary skill in the art, at the time the invention was made, would not have expected the claimed invention to be successful, as discussed further below.

The Ladner *et al.* reference, the only cited reference that pertains to intracellularly expressed libraries, provides no reasonable expectation of success that an intracellularly expressed polypeptide could achieve a ***functional*** interaction with a target binding protein. The DNA-DNA binding protein interactions taught by Ladner *et al.* all involve the ***direct binding*** of a protein to DNA. In the system taught by Ladner *et al.*, there is no requirement that the variegated portion of the proteins expressed in the library of Ladner *et al.* (*i.e.*, the mutated DNA binding domains) have any functional activity beyond binding to DNA. The ultimate ability of the library members to activate reporter gene expression resides in the transcriptional activation domain of the DNA binding protein, but this domain is not variegated. Thus, Ladner *et al.* teach methods of identifying DNA binding proteins of interest, which methods are all based on detecting a DNA ***binding*** interaction.

In contrast, the instant invention involves a ***functional interaction*** between an intracellularly expressed library polypeptide and a target orphan receptor. In accordance with the present invention, the library member not only interacts with, *e.g.*, bind to, the target orphan receptor, but also ***functionally*** interacts such that the receptor generates an intracellular signal that leads to a detectable signal. The ability to bind does not necessarily indicate the ability to functionally modulate. A showing that a polypeptide can bind to a target provides no reasonable expectation that the polypeptide can functionally modulate the target and thereby provide a detectable signal. Thus, Ladner *et al.* provides no reasonable expectation that the claimed invention, which involves a ***functional*** interaction between the test polypeptide and the orphan GPCR, could be successfully achieved.

Still further regarding the claim recitation that the test polypeptide be "transported to a location allowing interaction with the receptor expressed on the cell membrane", there was no reasonable expectation of success that this could be achieved for the system of the invention. Although there were examples in the art of the use of a signal sequence to direct secretion of a heterologous polypeptide in a host cell, the ability of any particular signal sequence to direct secretion of any particular heterologous polypeptide is highly variable and unpredictable. There are a number of factors that could have led to failure to

successfully transport the polypeptides to a location allowing interaction with the receptor expressed on the cell membrane. For example, fusion of a signal sequence could have altered the conformation of the signal sequence such that it no longer could mediate transport. Additionally or alternatively, fusion of a signal sequence could have altered the conformation of the potential orphan receptor ligands such that "true" ligands within the library could no longer functionally interact with the orphan receptor at the cell membrane. Still further, expression of the library of fusion polypeptides might have interfered with the normal workings of the transport pathway such that the library of polypeptides failed to reach a location that allowed for interaction with the orphan receptor. Accordingly, there was no reasonable expectation of success that test polypeptides could be successfully expressed in yeast such that they are "transported to a location allowing interaction with the receptor expressed on the cell membrane." GPCR expressed on the cell membrane of the yeast cells would provide a detectable signal.

Again, it must be emphasized that none of the five cited references is concerned with secretion of heterologous test polypeptides by yeast cells. In summary, there was no reasonable expectation of success in making the claimed recombinant cells that: 1) express a heterologous orphan GPCR "on the cell membrane of said cell such that signal transduction activity via said receptor is modulated by interaction with an extracellular signal"; 2) express a test polypeptide that "is transported to a location allowing interaction with the receptor expressed on the cell membrane"; and 3) collectively express a library of test polypeptides wherein "modulation of the signal transduction activity of the orphan cell surface receptor by one of said heterologous test polypeptides [within the library] that reacts with said orphan cell surface receptor will provide a detectable signal." For reasons discussed above, lack of any one of these functions is sufficient to create a lack of reasonable expectation of success for the claimed invention. Accordingly, in view of the numerous potential pitfalls discussed herein, there is no way that one can conclude that there was a reasonable expectation of success in making the claimed invention in view of the teachings of the cited references.

III. The Cited Art Does Not Teach or Suggest All of the Claim Limitations

Even if the cited references were combined in the manner proposed by the Examiner, this combination simply does not result in the claimed invention. To establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (see also M.P.E.P. 2143.03). In the instant situation, the methods recite that "the test polypeptide is *transported to a location allowing interaction with the receptor expressed on the cell membrane*" (emphasis added). This claim limitation is not taught or suggested by any of the cited references, alone or in combination. The Ladner *et al.* patent, which is the only one of the five cited references which is relied upon for teaching or suggesting expression of a heterologous polypeptide *in* a host cell, only teaches or suggests expressing the polypeptide intracellularly, to allow for interaction with a DNA binding protein that also is expressed entirely intracellularly. Thus, even if one were to combine the five cited references as proposed, this would not result in a method in which a test polypeptide is *transported to a location allowing interaction with the receptor expressed on the cell membrane.*

Applicants note that the foregoing arguments were made in parent application Ser. No. 08/582,333 to traverse the same obviousness rejection of corresponding method claims in the parent application under 35 U.S.C. §103 over the same five references, and were successful in obtaining allowance of corresponding method claims that issued as U.S. Patent 6,255,059. In particular, the Examiner's attention is invited to Applicants' responses filed January 12, 1998 and October 16, 1998, respectively, and the Notice of Allowance mailed in June 28, 1999 in the parent application. In fact, the method claims that were initially allowed [3] in the parent application recited the very recombinant yeast cells claimed in the instant application. Therefore, the claims of the instant invention should be patentable over the cited art under 35 U.S.C. §103 for the sames reasons as the claims in the parent application.

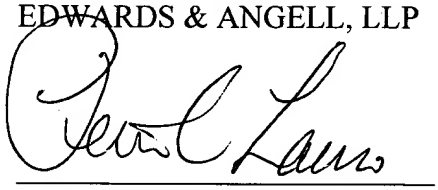
[3] In the parent application, Examiner Kaufman made a post-allowance rejection of the claims based on lack of utility in view of the recitation of "orphan receptor". An Examiner's amendment was subsequently filed to delete "orphan" from the claims that ultimately issued in 6,255,059.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of all pending rejections, and allowance of this application with claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78. If upon consideration of the foregoing arguments, the Examiner is not inclined to allow the application, Applicants respectfully request a personal interview with Applicants' attorney and invite the Examiner to call the undersigned at the telephone number indicated below.

Respectfully submitted,
EDWARDS & ANGELL, LLP



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